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Structure-Toxicity Relationships of Amyloid Peptide Oligomers

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1. Introduction

The accumulation of misfolded proteins as insoluble, fibrillar aggregates is characteristic of several degenerative diseases. Examples include the proteins involved in amyloid diseases such as Alzheimer's disease ($A\beta$) (Glennner and Wong 1984), type II diabetes (amylin) (Cooper et al. 1987) and Parkinson's disease (α -synuclein) (Spillantini et al. 1997), as well as the mammalian prion diseases (PrP) (Prusiner 1982). While infectivity and onset differ between amyloid and prion diseases, recent evidence suggests that soluble protein oligomers, rather than fibrils, are the cytotoxic species in each case (Lambert et al. 1998; Bucciantini et al. 2002; Kaye et al. 2003; Walsh and Selkoe 2004; Silveira et al. 2005; Baglioni et al. 2006; Simoneau et al. 2007). It has been suggested that these non-fibrillar assemblies may be a common element of all amyloid diseases, and non-fibrillar oligomers formed by several amyloid proteins have been identified *in vivo* or produced *in vitro*. Regardless of protein sequence, these oligomers share several key features, including reactivity to structural antibodies, the ability to permeabilize model membranes, and cytotoxicity to cultured neurons. However, despite their potential importance in the pathogenesis of amyloid diseases, the details of the molecular structure of these non-fibrillar oligomers are only now beginning to emerge, as is their relationship to mature fibrils, and to the onset of disease.

The mechanism or mechanisms through which these oligomeric species induce cell death and contribute to the pathology of amyloid diseases remain a matter of some debate. Current hypotheses include a physical disruption of cellular membranes, formation of amyloid pores or channels, induction of oxidative stress, or interactions with receptor proteins on the cell surface leading to either altered protein function, or the initiation of a signaling event. Defining the link between the structure of misfolded protein aggregates and the concurrent gain of a toxic functionality is inhibited by the inherent difficulties of studying aggregative proteins, and is further complicated by the ability of amyloid proteins and peptides to form several distinct types of oligomers and fibrils, which often exist as heterogeneous mixtures. Each species of aggregate may exhibit varied biological activity, different local structure or gross morphology and typically contains different numbers of monomers per assembly. Despite these challenges, there has been significant recent progress in obtaining high-resolution structural details of amyloid fibrils and non-fibrillar oligomers, and in defining their biological mode of action. In this chapter, we review the current knowledge of the structure-toxicity relationship of non-fibrillar amyloid oligomers.

2. Amyloid fibrils

2.1 Overview of amyloid fibril structure

As the final stage in the assembly pathway for misfolded amyloid proteins, accumulation of fibrils has long been seen as the hallmark of amyloid diseases. Since they were the only readily detectable amyloid assembly present in disease tissue, early work suggested that fibrils were likely to be the mediators of cell death and disease progression. In addition, preparation of stable mature amyloid fibrils has generally been more accessible than the potentially transient non-fibrillar oligomers, facilitating biophysical and structural analysis. With recent advances in methodology and instrumentation, high-resolution structural details have been reported for amyloid fibrils formed by several proteins and peptides, based on data from crystallographic and solid state (nuclear magnetic resonance) NMR studies (Petkova et al. 2002; Jaroniec et al. 2004; Sawaya et al. 2007; Lee et al. 2008; 2009). While the details of each structure differ, based on sequence and solution conditions used for assembly, these studies have confirmed the presence of a cross- β architecture within the core of all amyloid fibrils studied to date. This structural motif is characterized by having protein or peptide strands form extended β -sheets running perpendicular to the long axis of the filament, and was initially identified from x-ray fiber diffraction studies of amyloid fibrils (Eanes and Glenner 1968; Geddes et al. 1968; Jahn et al. 2009). The cross- β diffraction pattern contains intense reflections at 4.7-4.8 Å (meridional) and 10 Å (equatorial) due to the characteristic spacing between β -strands along the long axis and between the perpendicularly stacked β -sheets, respectively.

In general, the core of most amyloid fibrils is considered to contain a dehydrated interface between adjacent β -sheets. This is typically considered to result from packing of hydrophobic residues in a water-excluded core, giving rise to one of 8 possible steric zipper arrangements, as first proposed by Sawaya *et al.* (Sawaya et al. 2007) (Figure 1A). These permutations arise from the fact that there are 2 possible types of β -sheet (parallel or antiparallel), 2 stacking possibilities (parallel or anti-parallel) and 2 surfaces for inter-sheet packing (face-to-face or face-to-back). The presence of steric zipper motifs was initially observed in X-ray structures of fibril-like crystals formed by short amyloidogenic peptides (Sawaya et al. 2007), and a subset of these classes of intersheet packing have been observed in solid-state NMR structures of amyloid fibrils (Nielsen et al. 2009). It is important to note, however, that recent NMR studies have revealed some possible structural differences between the crystalline and fibrillar forms of the GNNQQNY peptide derived from the yeast prion Sup35 (van der Wel et al. 2007), such that more structures of amyloid fibrils are required to confirm the crystallographic data.

Additional complexity in fibril structure comes from quaternary interactions in which protofilaments containing a basic building block (for example a filament formed by extended arrangement of a pair of stacked β -sheets) are bundled or twisted together to form the mature amyloid fibril. It is clear from electron microscopy studies of fibrils formed by numerous amyloid peptides that significant heterogeneity can exist between fibrils formed by the same peptide (Fandrich et al. 2009). This can be rationalized as variations in the interchain, intersheet, and interprotofilament packing, as well as conformational heterogeneity between peptide chains. The heterogeneous nature of many fibril preparations has been supported by solid state NMR for A β (1-40) (Petkova et al. 2005), α -synuclein (Heise et al. 2005), GNQQNY fibrils (van der Wel et al.), and amylin (Madine et al. 2008).

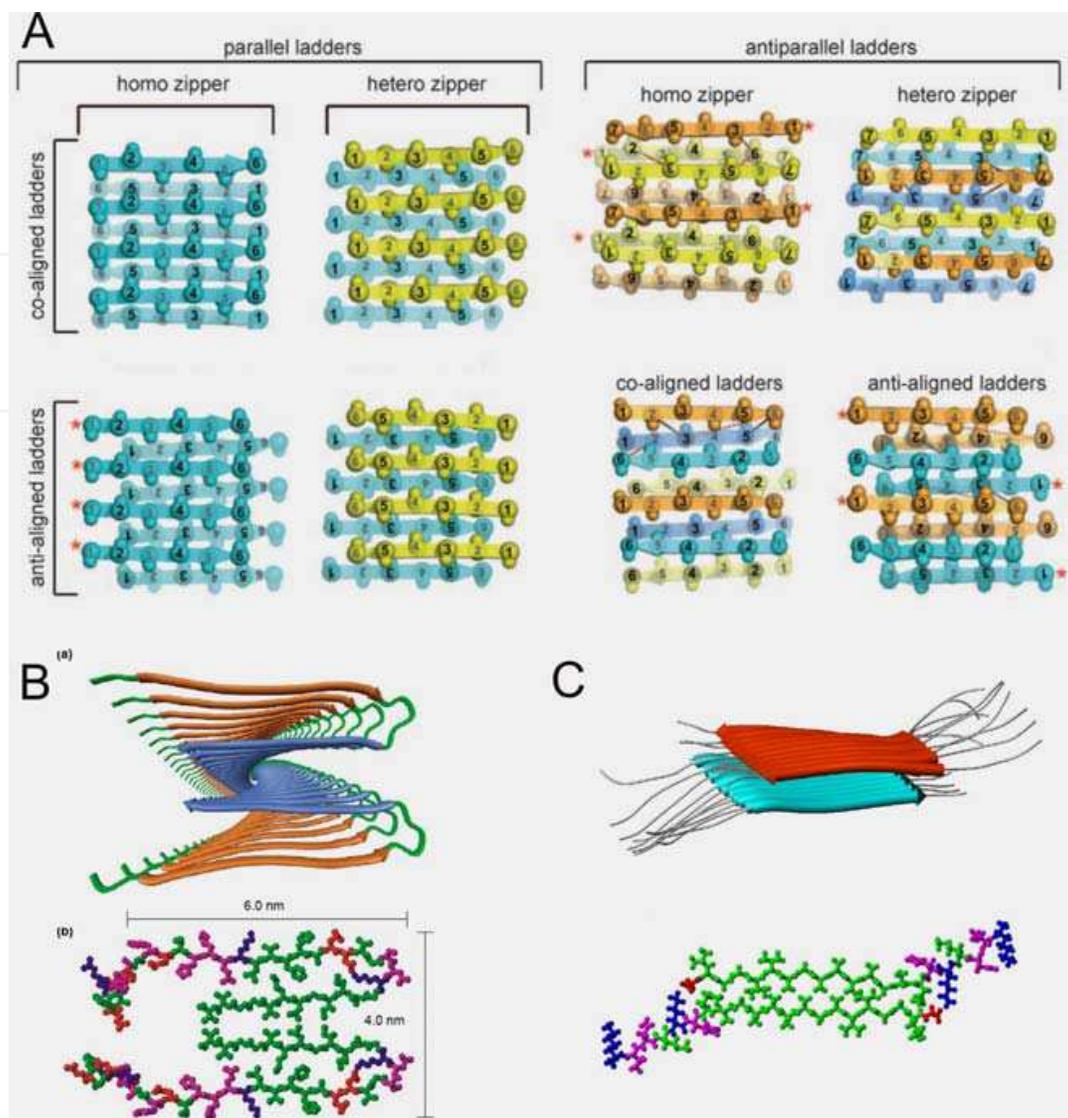


Fig. 1. Structural models for amyloid fibrils. (A) Possible arrangements of beta-strands in an amyloid fibril. Eight permutations exist, four containing parallel β -sheets and four containing anti-parallel β -sheets, each with the possibility of parallel or antiparallel stacking of the two sheets, which may align in a face-to-face or face-to-back manner. In each case, the interface between the sheets forms a so-called steric zipper, with opposing side chains interdigitating to exclude water. Reprinted with permission from Nielsen *et al.*, 2009. Copyright 2009 Angewandte Chemie. (B) Structural model for A β (1-40) fibrils, as determined by solid state NMR. This structure contains a class 1 steric zipper with parallel β -sheets stacked in a face-to-face antiparallel arrangement. The upper image shows the backbone of several monomers, arranged with the fibril axis extending into the page, while the lower image focuses on a representative pair of peptides, showing the interdigitation of sidechains within the hydrophobic core, as well as depicting quaternary contacts between adjacent protofilaments. Reprinted with permission from Petkova *et al.*, 2002. Copyright 2002 Proceedings of the National Academy of Science of the United States. (C) Structural model for amyloid fibrils formed by PrP(106-126), determined using solid state NMR. The peptide strands are arranged in a class 1 steric zipper motif with a salt bridge between K110 and the carboxylate of the C-terminus. The overall structural effect is similar to a single layer of the A β structure. Reprinted with permission from Walsh *et al.*, 2009. Copyright 2009 Structure

Probably the best characterized fibril structures are those formed by fragments of the Alzheimer's A β protein. In particular, several structures for fibrils formed by A β (1-40) have been reported, based primarily on solid state NMR or transmission electron microscopy (TEM) (Chan 2011; Tycko 2011; Petkova et al. 2002; Sachse et al. 2008). The fibril morphology and subunit peptide structure in each case is dependent on the incubation conditions during *in vitro* fibrillization, and can exhibit significant heterogeneity in both TEM and NMR experiments. An example structure for A β (1-40) fibrils is shown in Figure 1B. Each peptide adopts a β -turn- β conformation, forming parallel in-register β -sheets with neighboring peptides down the long axis of the fibril. The two sheets pack into an internal class 1 steric zipper motif within the protofilament. In this structural model, quaternary interactions between two protofilaments were determined using intermolecular dipolar couplings from solid state NMR, giving rise to the depicted structure for the mature fibril. These quaternary interactions vary between fibrils with different morphology, such as the three-fold symmetric fibrils reported by Paravastu *et al.*, (Paravastu et al. 2006) or those studied by cryoelectron microscopy (Sachse et al. 2008; Schmidt et al. 2009).

By contrast, only a single well-defined structure has been reported so far for protofilaments formed by the far more neurotoxic and more aggregative A β (1-42) peptide, which is a less abundant form of A β , but which correlated more closely with pathogenesis (Burdick et al. 1992; Jarrett et al. 1993; Luhrs et al. 2005; Kumar-Singh et al. 2006). This structure is similar to that of A β (1-40), but rather than intramolecular contacts forming the steric zipper, the top strand from one monomer makes side chain contacts with the bottom strand from an adjacent monomer. Modeling of the mature fibril based on cryoelectron microscopy and hydrogen/deuterium exchange measurements has suggested a distinctly different quaternary assembly for A β (1-42) fibrils, but the potential relationship between these structures and the varied biological activity of the two A β peptides remains (Miller et al.; Olofsson et al. 2007; Zhang et al. 2009).

Numerous solid state NMR structures of small amyloid-forming peptides have now been reported, including short fragments of A β (Balbach et al. 2000; Tycko and Ishii 2003), amylin (Luca et al. 2007; Madine et al. 2008), transthyretin (Jaroniec et al. 2002; Jaroniec et al. 2004), calcitonin (Naito et al. 2004) and neurotoxic fragments of PrP (Cheng et al. 2011; Lee et al. 2008; 2009). As shown for PrP(106-126) fibrils in Figure 1C, most of these structures reflect similar architecture as observed for A β , parallel β -sheets and a class 1 steric zipper packing. Some short peptides display alternate packing arrangements in the fibrils, such as the antiparallel β -sheets formed by A β (16-22) (Balbach et al. 2000) or the antiparallel heterozipper arrangement of amylin(20-29) fibrils (Nielsen et al. 2009). Longer amyloid proteins have remained more challenging. For example, initial studies of full-length α -synuclein by hydrogen–deuterium exchange and solid state NMR have allowed identification of secondary structure elements and delineation of the fibril core, but a high-resolution fibril structure is lacking (Heise et al. 2005; Vilar et al. 2008).

2.2 Prion fibrils

The prion protein (PrP) is the major causative agent of neurodegenerative prion diseases, such as scrapie in sheep, BSE in cattle, and CJD among others in humans. The protein converts from a monomeric, primarily helical cellular form (PrP^C), to an infectious, oligomeric, scrapie form (PrP^{Sc}), with increased β -structure. In addition, there are several known fungal prion proteins, unrelated to PrP in amino acid sequence, but sharing the

ability to adopt a fibrillar, infectious, β -sheet rich structure. While sharing some common structural elements with fibrils formed by amyloid proteins, some striking differences have been observed. For example, the fungal Het-S prion protein structure solved by solid state NMR contains a β -solenoid structure with two protein molecules per “rung” of the solenoid ladder, rather than the cross- β packing typical of amyloid (Figure 2) (Wasmer et al. 2008). By contrast, amyloid fibrils formed by PrP *in vitro* were shown by electron paramagnetic resonance (EPR) to contain amyloid-like in-register parallel beta-sheet structure (Cobb et al. 2007) (Figure 2), similar to the yeast prion proteins Ure2 (Baxa et al. 2007) and Sup35 (Shewmaker et al. 2006). Interestingly, it has been shown through electron crystallography, X-ray fibre diffraction, and molecular dynamics simulations that the infectious PrP^{Sc} form of PrP from infected brains likely differs from *in vitro* fibrils and may contain a β -helix or β -solenoid structure (Govaerts et al. 2004), similar to Het-S.

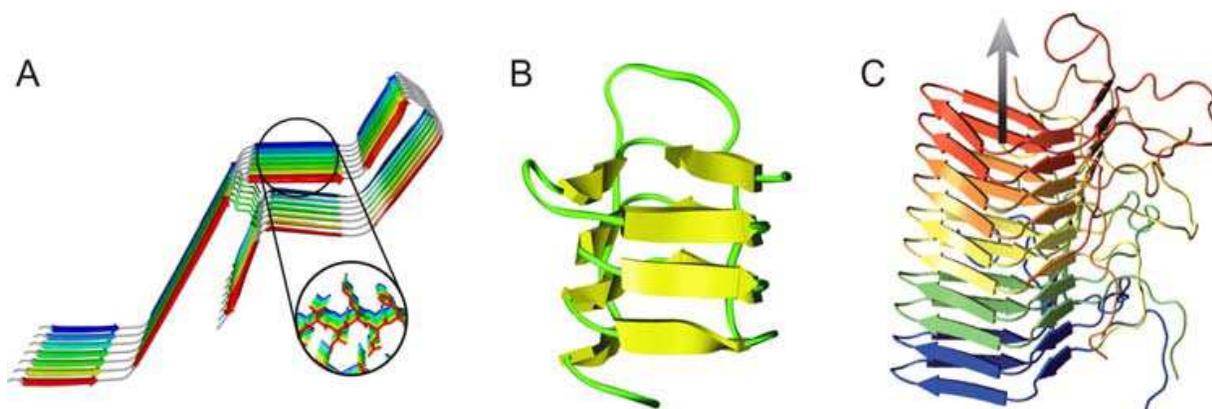


Fig. 2. Structures formed by prion proteins from human and yeast systems. (A) Structure of amyloid fibrils formed by PrP, showing parallel in-register β -sheets. The structure is also stabilized by a disulphide bond. Reprinted with permission from Cobb *et al.*, 2007. Copyright 2007 Proceedings of the National Academy of Science of the United States. (B) β -helical structure formed by human PrP taken from infectious material. Reprinted with permission from Govaerts *et al.*, 2004. Copyright 2004 Proceedings of the National Academy of Science of the United States. (C) The Het-S prion structure from solid state NMR showing residues 218-289 in a β -solenoid. Reprinted with permission from Wasmer *et al.*, 2008. Copyright 2008 Science

3. Non-fibrillar amyloid oligomers

3.1 Overview

While a wealth of structural information is becoming available for the fibrillar forms of many model and disease related amyloid proteins and peptides, relatively little is known about the molecular structure of non-fibrillar oligomers formed by the same polypeptides. Structural characterization has been made particularly challenging by the transient nature of many of these assemblies, which are widely considered to form as intermediates along the amyloid misfolding pathway. Thus, the difficulty of obtaining highly pure samples of non-fibrillar oligomers which are sufficiently long-lived for biophysical studies has significantly slowed progress in this field. A number of studies have used small molecules, including detergents or lipids, to trap or stabilize oligomeric states of amyloid proteins (Laurents et al. 2005; Yu et al. 2009), but this approach risks formation of off-pathway or non-productive

assemblies, rather than the on-pathway intermediates likely to play a role in amyloid disease (Kayed et al. 2003).

Despite these challenges, however, a number of low-resolution studies have been reported, using TEM, atomic force microscopy (AFM), hydrogen/deuterium exchange, and fluorescence spectroscopy-based approaches (Huang et al. 2000; Williams et al. 2005; Losic et al. 2006; Ono et al. 2009). Microscopy and size exclusion chromatography have shown that, similar to amyloid fibrils, there are a wide range of non-fibrillar oligomers that can be categorized based on their size (ranging from dimers of A β (1-40) to large globular assemblies containing hundreds of peptide monomers) or morphology (Haass and Selkoe 2007; Walsh and Selkoe 2007). In terms of the latter, most oligomers reported have either exhibited a roughly globular appearance by AFM and TEM, or have been annular in nature – exhibiting a pore or ring shaped structure (Janson et al. 1999; Conway et al. 2000; Lashuel et al. 2002). These two morphologies appear to exhibit different degrees of biological activity, with spherical oligomers, but not annular oligomers, increasing membrane conductance and inducing apoptosis in cell culture (Kayed et al. 2009). The large (3-10 nm diameter), spherical oligomers formed by several amyloid proteins have been shown to bind to a single conformational antibody, suggesting that a common structural motif exists in these assemblies, despite having no sequence similarity. Antibody binding was also shown to inhibit the inherent cytotoxicity of these large amyloid oligomers (Figure 3). Likewise, annular oligomers formed by A β (1-42), amylin and α -synuclein are all recognized by an antibody that does not bind to monomeric or fibrillar material, and that shows only weak binding to spherical oligomers, indicating that these contain distinct structural elements from the other assemblies (Kayed et al. 2009).

More recently, solid state NMR has been successfully used to obtain high-resolution structural details of non-fibrillar oligomers formed by A β (Chimon and Ishii 2005; Chimon et al. 2007), PrP(106-126) (Walsh et al. 2009; Walsh et al. 2010), and α -synuclein (Kim et al. 2009), and solution NMR has been used to investigate the structure of small detergent stabilized oligomers of A β (1-42) (Yu et al. 2009). Advances in computational infrastructure and methodologies have also led to an increased use of molecular dynamics simulations to investigate the structure and assembly of non-fibrillar amyloid oligomers.

3.2 A β oligomers

The non-fibrillar oligomers formed by A β (1-40) and A β (1-42) have been implicated as the main toxic species associated with Alzheimer's disease, and as such have been the focus of the majority of studies on amyloid oligomers reported to date. Structural characterization has been impeded by the wide spectrum of oligomeric states that can be adopted by these peptides along their aggregation pathways. As indicated above, species ranging in size from dimers to oligomers containing hundreds of peptides have been reported, both *in vitro*, and in material isolated from the brains of Alzheimer's patients (Haass and Selkoe 2007; Walsh and Selkoe 2007).

The larger oligomers can also be subdivided into spherical, so-called pre-fibrillar oligomers and ring-shaped annular oligomers, each with different antibody reactivity. From a high-resolution standpoint, most experimental progress has been made in defining the molecular structures of small and large pre-fibrillar oligomers formed by A β , although numerous molecular dynamics simulations have been carried out on membrane-bound amyloid channels or pores that closely resemble the overall morphology of annular protofibrils as

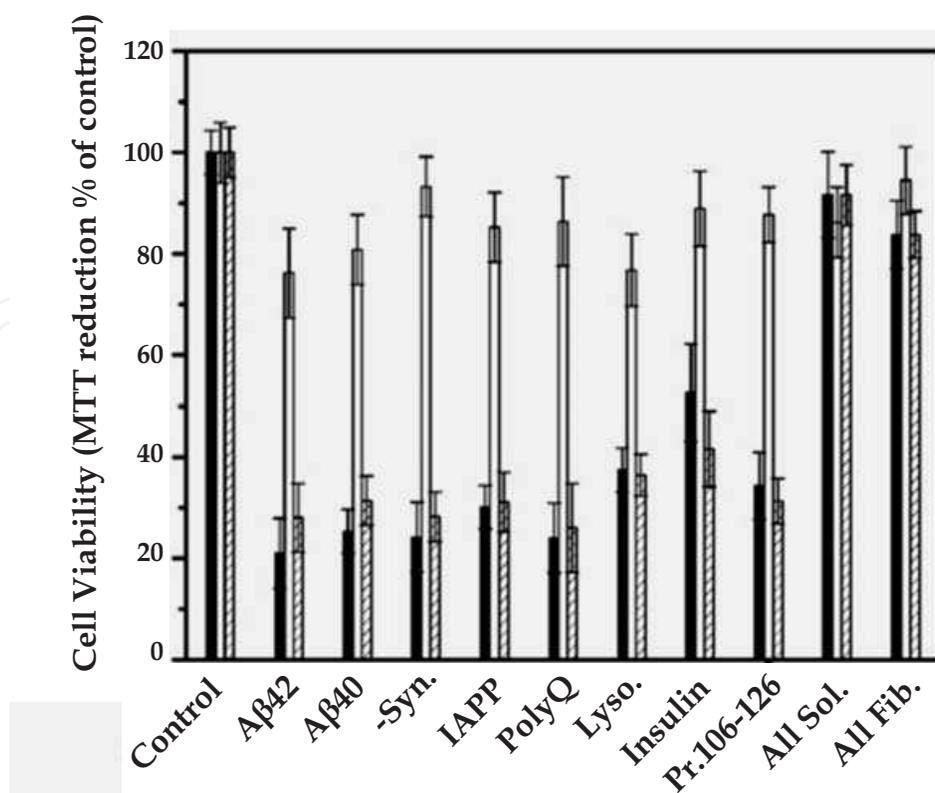


Fig. 3. Amyloid oligomers are toxic and share a common structural element. A graph showing the viability of neuroblastoma SH-SY5Y cells, monitored by the 3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyltetrasodium bromide (MTT) reduction assay, as a function of treatment with preparations of several amyloid proteins. The toxicity of non-fibrillar oligomers formed by each peptide is shown to significantly decrease cell survival (black bars) relative to the control, soluble (presumed monomeric) peptide and mature amyloid fibrils. In each case, the effects of the oligomers on cell survival are attenuated by the addition of an amyloid oligomer specific antibody (A11, white bars). Non-specific IgG is shown in hatched bars, and exerts no effect on the system. Reprinted with permission from Kaye *et al.*, 2003. Copyright 2003 Science

seen in TEM and AFM images (Jang *et al.* 2007; Zheng *et al.* 2008). These annular oligomers are 8-20 nm in diameter by TEM and AFM, and like the spherical oligomers, circular dichroism (CD) spectroscopy shows that they contain high levels of β -sheet (Kayed *et al.* 2008). The anti-annular oligomer antibodies also bind to the β -barrel pores formed by the bacterial toxin α -hemolysin, such that they may share the same general architecture (Kayed *et al.* 2009). Interestingly, preformed annular oligomers did not permeabilize membranes, instead converting to prefibrillar oligomers upon interaction with membranes. This may suggest that any pore like structure formed by A β would need to assemble within the membrane, rather than acting through insertion of a preformed assembly.

In the pre-fibrillar oligomers, the structural data that has emerged from recent studies suggests that even at the earliest stages of aggregation they share common features with the fibrillar forms of A β . For example, Yu *et al.*, used 0.05% SDS to stabilize very small pre-globulomers and globulomers of A β (1-42), with molecular weights of 16 and 64 kDa respectively (Yu *et al.* 2009). These were assumed to represent very early points in the amyloid aggregation pathway, and structural studies were conducted using solution NMR.

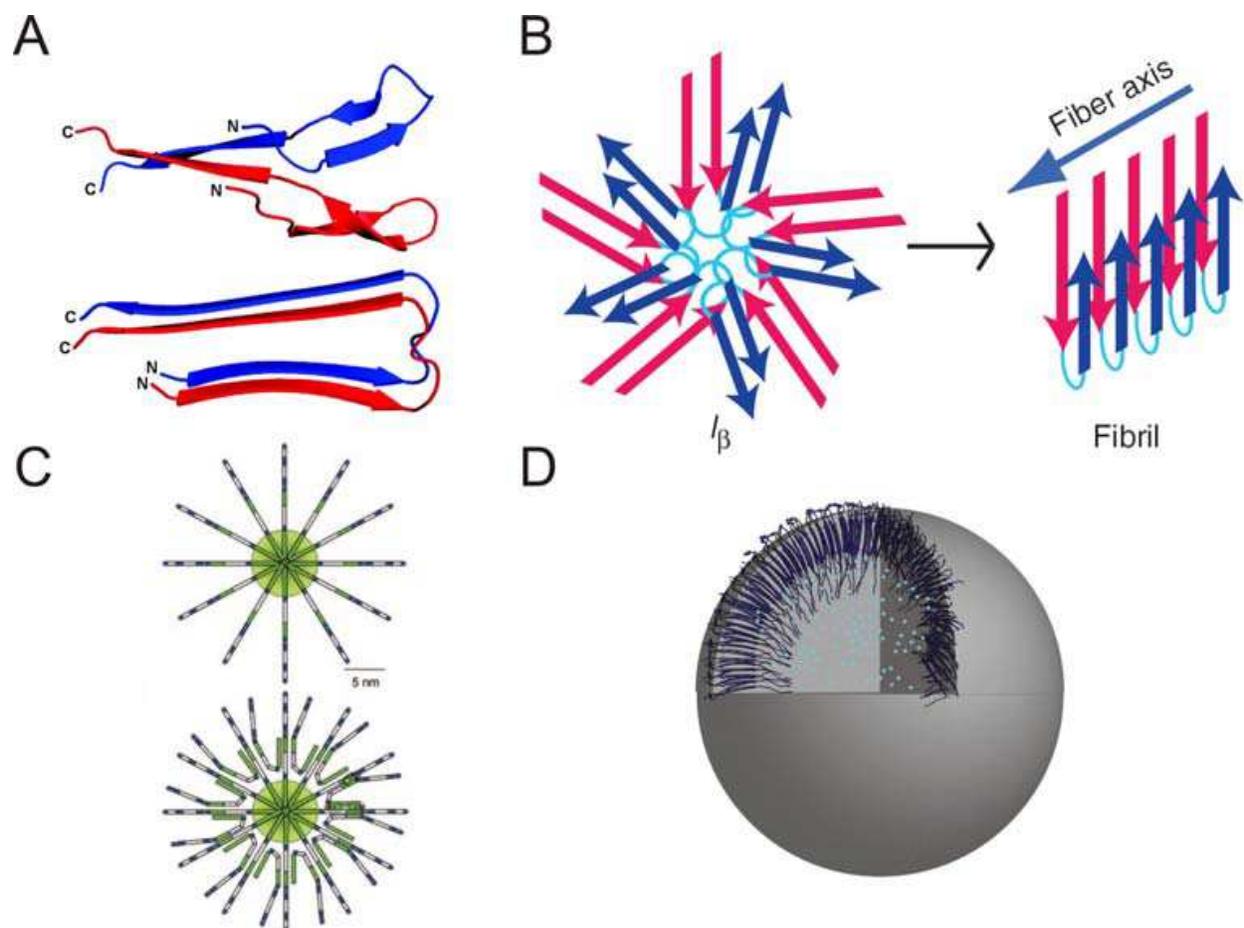


Fig. 4. Structures of non-fibrillar amyloid oligomers. (A) Pre-globulomer (top) and globulomer (bottom) structures formed by A β (1-42) are shown. Both structures show similarities to the basic A β (1-40) fibril subunit shown in Figure 1B. Reprinted with permission from Yu *et al.*, 2009. Copyright 2009 The American Chemical Society. (B) Structural model of large spherical A β (1-40) oligomers obtained using solid state NMR. Reprinted with permission from Chimon *et al.*, 2008. Copyright 2008 Nature Publishing Group. (C) A structural model of large, DSS stabilized A β (1-40) oligomers shown as extended micelle-like structures, approximately 35nm in diameter. Significant structural similarity with the solid state NMR derived model shown in (B) is evident. Reprinted with permission from Laurents *et al.*, 2005. Copyright 2005 Journal of Biological Chemistry. (D) A structural model for non-fibrillar PrP(106-126) oligomers, obtained from solid state NMR, showing similar contacts to those seen in fibrils formed by the same peptide (Figure 1C). The basic subunit is a parallel beta sheet stacked two high to form a class 1 steric zipper which are arranged in a micelle-like formation. Reprinted with permission from Walsh *et al.*, 2010. Copyright 2010 The American Chemical Society

The intra-chain and inter-chain contacts in these oligomers share similarities with the A β (1-40) and A β (1-42) fibril structures reported to date. Both contain similar secondary structure elements with the fibrillar form, and contain intermolecular contacts reminiscent of the fibrils, although in the small oligomers, the N-terminal strand folds back on itself, rather than participating in intermolecular β -sheet formation (Figure 4A). In a similar vein, DSS was used to stabilize very large (764 kDa) A β (1-40) oligomers, and subsequent structural analysis suggested the presence of micelle-like assemblies containing a radial

arrangement of A β monomers in an extended β -sheet conformation (Figure 4C) (Laurents et al. 2005). The nature of intermolecular or intramolecular β -sheets was not determined in this study, so it is difficult to relate the resulting models to the fibrillar form of the protein.

For both of the aforementioned studies, it is important to note that the effect of detergents and other small molecules on the structure and assembly of amyloid peptides remains unclear. Addition of cofactors may lead to formation or stabilization of otherwise unpopulated structures. Recent studies of on-pathway prefibrillar oligomers of A β (1-40) and A β (1-42) have circumvented this requirement by using either gel filtration and lyophilization (Chimon and Ishii 2005; Chimon et al. 2007) or careful modulation of solution salt and pH conditions to trap non-fibrillar oligomers for structural studies (Ahmed et al. 2010).

Solid state NMR of large (15-35nm) spherical oligomers of A β (1-40) prepared by freeze-trapping revealed fibril-like secondary and quaternary structures, leading to a model in which the location and intermolecular assembly of β -sheets is shared between the two forms (Chimon et al. 2007). A schematic for the proposed architecture of these oligomers is shown in Figure 4B, along with a model of the A β (1-40) protofilament structure determined by Petkova *et al.* (Petkova et al. 2002). This micelle-like arrangement is reminiscent of that proposed for DSS-stabilized oligomers (Figure 4C), potentially validating the use of small molecules to trap transient amyloid oligomers. These large oligomers were shown to exhibit neurotoxicity, and based on their transient nature can be assumed to lie on the fibril assembly pathway.

Ahmed *et al.* have used altered solution conditions to trap discoidal pentamers and decamers of A β (1-42) with potent neurotoxicity (Ahmed et al. 2010). When incubated at 37°C for several hours, these oligomers convert to amyloid fibrils, suggesting that they are productive intermediates on the assembly pathway. In contrast to the large A β (1-40) oligomers studied by Chimon *et al.* (2007), Fourier-transform infrared (FTIR) spectroscopy and solid-state NMR studies of these small oligomers indicated the presence of significantly increased disorder and solvent accessibility relative to fibrils of A β (1-42), and showed that the oligomers lack the in-register parallel β -sheet architecture of the fibrillar form. The oligomeric peptides do, however, contain the same β -loop- β secondary and tertiary fold observed in A β (1-42) and A β (1-40) fibrils. This is supported by molecular dynamics and hydrogen-deuterium exchange studies from several other groups, and leads to an overall picture in which A β peptides adopt a β -loop- β structure as a common element of all oligomeric states, with intermolecular contacts and solvent accessibility varying between different types of oligomers. MD and H/D exchange studies support these conclusions, leading to the general concept that early intermediates formed during A β assembly may be more solvent accessible and potentially more labile, and that conformational flexibility is likely to play an important role in their biological activity (Pan et al. 2011; Yu et al. 2010; Yu and Zheng 2011; Cheon et al. 2007; Zhang et al. 2009).

3.3 PrP(106-126) oligomers

The PrP derived peptide PrP(106-126) poses an interesting structure-toxicity relationship. Evidence has been presented both in favour of, and against, a dependence of PrP(106-126) toxicity on expression of cell-surface full length PrP (Brown 1998). However, it has also been shown that this PrP derived peptide is able to form both amyloid fibrils and cytotoxic oligomers, making it a useful model for studying the structural and mechanistic details of non-fibrillar amyloid oligomers (Forloni et al. 1993; Selvaggini et al. 1993; Jobling et al. 1999;

Salmona et al. 1999). For example, in studies by Kaye *et al.*, non-fibrillar oligomers of PrP(106-126) were shown to form large (10-20nm diameter) spherical oligomers with similar morphology to A β , amylin, and several other amyloid proteins (Kayed et al. 2003). These oligomers cause increase membrane conductance and were cytotoxic to neuronal cell cultures, and have also been shown to disrupt model-membranes in a concentration dependent manner, as revealed by a liposome dye-release assay (Kayed et al. 2004; Walsh et al. 2009). Utilizing solid state NMR, a structural model was developed for these non-fibrillar oligomers (Figure 4D) (Walsh et al. 2010). Similar to the A β (1-40) oligomers reported by Ishii *et al.* (Chimon et al. 2007), large PrP(106-126) oligomers contain fibril-like secondary structure and intermolecular contacts, suggesting that they are composed of small fibril-like segments arranged in a micelle-like assembly. This is an interesting observation considering that these oligomers do not bind thioflavin-T, unlike the amyloid fibrils formed by PrP(106-126), implying that the oligomers either lack the extended cross- β structure required for dye-binding, or that the binding site for the dye is occluded in the oligomer structure.

3.4 α -synuclein oligomers

In the case of α -synuclein, despite its innate lipid binding ability, it is the aggregated state that is considered to gain cytotoxic function, likely acting through membrane permeabilization (Haass and Selkoe 2007). Strong evidence has been presented to suggest that oligomers lying on misfolding pathway leading to amyloid fibril formation are the most cytotoxic species formed by this protein (Lashuel et al. 2002). These oligomers were found to share common structural elements with other amyloid oligomers as seen by A11 antibody binding (Kayed et al. 2007), and the presence of extensive β -sheet secondary structure in baicalin stabilized oligomers has been confirmed through FTIR and CD spectroscopy (Zhu et al. 2004; Hong et al. 2008). A recent study combined biophysical analysis with solution and solid state NMR to more closely investigate the structure and membrane interaction of non-fibrillar α -synuclein oligomers (Kim et al. 2009). Through solid state NMR it was shown that the pore forming contained β -sheet secondary structure but that there were significant differences between the structures of the monomeric, oligomeric and fibrillar states of this protein - contrasting with the studies of A β and PrP(106-126) oligomers referenced above.

3.5 Other amyloid oligomers and common structural elements

While several other amyloid proteins and peptides, including amylin and polyglutamine, have been shown to form neurotoxic, non-fibrillar oligomers, there is currently no high-resolution structural information available on these systems. It is known that at least one oligomeric state populated by each peptide is morphologically similar to that observed for spherical aggregates of A β , PrP(106-126), and α -synuclein. These oligomers also cause increased membrane permeability (Kayed et al. 2004; Demuro et al. 2005), and furthermore share the common structural element that allows recognition by the A11 anti-oligomer antibody developed by Kaye *et al.* (Kayed et al. 2003).

In the case of the mammalian prion protein, non-fibrillar oligomers of various sizes have been identified and shown to be neurotoxic (Baskakov et al. 2002; Sokolowski et al. 2003; Silveira et al. 2005; Simoneau et al. 2007). Small oligomers (composed of < 30 monomers) of PrP purified from the brains of infected animals have been shown to be the most infectious and toxic form of the protein, echoing the biological activity of amyloid oligomers (Silveira

et al. 2005). PrP oligomers have been shown to contain a predominantly β -sheet secondary structure by FTIR spectroscopy and CD, but no detailed structural information has been reported (Baskakov et al. 2001; Sokolowski et al. 2003). Of particular interest, the population of a β -sheet rich octamer formed during the misfolding of PrP has been shown to correlate with the susceptibility of different mammals to prion disease, further highlighting the role of oligomeric species in pathogenesis (Khan et al. 2010).

3.6 Where do non-fibrillar oligomers fit into the misfolding pathways of amyloid proteins?

The relationship between the formation of non-fibrillar oligomers and the misfolding pathway leading to amyloid fibril formation has not been definitively determined. While there have been conflicting reports (Necula et al. 2007), most evidence points to the spherical, cytotoxic oligomers existing as on-pathway intermediates. In particular, various prefibrillar oligomers of A β have been shown to be transient, disappearing as they reorganize into mature fibrils (Chimon and Ishii 2005). Similarly, pore forming oligomers of α -synuclein are considered to be on-pathway for fibrillization (Kim et al. 2009). From a mechanistic standpoint, the structural data on prefibrillar oligomers suggests early adoption of an extended β -structure, followed by formation of tertiary and quaternary contacts as the oligomers increase in size. The precise steps involved in the transition from discoidal or spherical oligomers to an extended amyloid fibril have not been determined, but likely involve an increase in the tightness of lateral associations between strands, with optimized hydrophobic packing and hydrogen bond formation driving the final steps of assembly. Taken together, the transient nature and fibril-like structure show that these entities exist on the aggregation pathway toward fibril. As described above, annular oligomers do not appear to exist as productive intermediates, but may instead represent off-pathway assembly. In the case of A β , it has been shown that in the presence of lipid membranes, prefibrillar oligomers are capable of rearranging to form annular oligomers, suggesting that in this case they may represent an alternate end-stage of the misfolding pathway (Kayed et al. 2009). This may also present a possible mechanism for formation of membrane-disrupting entities from the on-pathway non fibrillar oligomers, as discussed below.

4. Non-fibrillar amyloid oligomers as the cytotoxic agents in amyloid disease

While early studies focused on the amyloid fibrils or plaques as the causative agents of neurotoxicity in Alzheimer's disease, more recently it has become evident that small non-fibrillar oligomers correlate much more closely with loss of neuronal function and neurodegenerative disease progression (Kayed et al. 2003; Haass and Selkoe 2007; Walsh and Selkoe 2007). This finding has been echoed for non-fibrillar oligomers formed by a broad array of disease related and non-disease related amyloid proteins (Baglioni et al. 2006). Given the potential for some amyloid oligomers to have similar structural properties, regardless of amino acid sequence, it is possible that many of these may act via a similar toxic mechanism. The conformations accessible to aggregative proteins may create interactions with components of the cellular ion transport system or may allow them to form channels or pores in cell membranes (Lin et al. 2001; Kayed et al. 2004; Demuro et al. 2005). This may represent a general mechanism through which cytotoxic effects are exerted during the early stages of protein aggregation. Supporting this hypothesis, soluble amyloid oligomers with spherical morphology, induce vesicle leakage, and are toxic to cultured cells,

possibly through disruption of calcium homeostasis (Thellung et al. 2000; Demuro et al. 2005; Ferreira et al. 2008).

Alternatively, hydrophobic, misfolded proteins are likely to have a high propensity to associate with membranes, and membrane binding of many amyloid peptides has been described extensively (McLaurin and Chakrabartty 1996; Yip et al. 2002; Kaye et al. 2004). Once bound to the membrane surface, or inserted into the bilayer, non-fibrillar oligomers would have the potential to rearrange into channels, pores, or non-specific aggregates at the membrane surface. Any of these mechanisms are likely to cause membrane destabilization and cell death, and it has recently been demonstrated for A β oligomers that increased membrane conductance can occur in the absence of channel formation (Sokolov et al. 2006). Physical disruption such as the introduction of membrane defects, possibly through insertion of oligomers, or through membrane-catalyzed fibril formation, would also be sufficient to induce leakage of cell contents and ultimately lead to cell death (McLaurin and Chakrabartty 1997; Yip et al. 2002).

While the oligomer fold is distinct from that of fibrils, as determined by differential antibody reactivity, a common theme emerging from structural studies of non-fibrillar amyloid oligomers is the presence of local fibril-like structure. While it does not speak to the actual mechanism through which toxicity is exerted, this observation may suggest that small fibril-like assemblies are the key element required for cytotoxicity. A similar phenomenon has been reported by Xue *et al.* (Xue et al. 2009), who demonstrated that fragmentation of mature amyloid fibrils formed by α -synuclein, β 2-microglobulin and lysozyme leads to an increase in membrane disruption and cytotoxicity (Figure 5). Likewise amyloid fibrils formed by hexapeptides gained cytotoxicity towards primary neuronal cell culture after physical disruption (Pastor et al. 2008). In both studies, it is likely that the increase in active ends allows improved interactions with cellular targets – membranes or other cell surface molecules, where they are able to rearrange to form active, toxic entities. Oligomeric species, which are known to be more conformationally flexible and less stable than their fibrillar counterparts, may act through a similar mechanism, carrying active fibril-like segments to the site of toxic activity.

4.1 A β toxicity

As with molecular structure, the link between oligomerization of an amyloid protein and disease progression has been explored in detail for A β . Several lines of evidence support a role for oligomers as the toxic entity in Alzheimer's patients. Anti-oligomer antibodies stain diffuse amyloid in human brains, showing that soluble oligomers with similar structural properties as those formed *in vitro* exist *in vivo* (Kaye et al. 2007). In addition, both injection of *in vitro* formed oligomers into brain tissue, and reinjection of small soluble A β oligomers isolated from diseased animals are able to induce loss of synaptic function and neuronal death (Walsh and Selkoe 2004; Cleary et al. 2005; Haass and Selkoe 2007; Walsh and Selkoe 2007). This experiment has also been performed for non-disease causing amyloid proteins, supporting a role for other amyloid oligomers as *in vivo* cytotoxins (Baglioni et al. 2006).

A β oligomer toxicity *in vitro* has been attributed to several distinct mechanisms, including but not limited to, membrane disruption and the direct formation of ion channels. Certainly there have been numerous reports of increased membrane conductance or leakage in the presence of A β oligomers ranging from small globulomers to large prefibrillar assemblies (Chimon and Ishii 2005; Yu et al. 2009), with some evidence presented to support formation of discrete ion channels or pores (Arispe 2004; Quist et al. 2005). A lot of attention has been

focused on the latter, and several molecular modeling studies have proposed models for the structure of a putative pore or channel – typically a picket-fence arrangement of monomers adopting the β -loop- β structure from the fibril structures (Jang et al. 2007). Alternatively, alteration of the mechanical properties of the membrane could lead to increased conductance as observed by Sokolov *et al.* (Sokolov et al. 2006), although the structural basis for this is unclear.

Several very specific proposals for A β oligomer toxicity have been proposed as alternatives to membrane disruption. As a group these invoke interactions with specific cell-surface targets, with subsequent alteration of normal protein activity leading to loss of neuronal function and possibly to cell death (Verdier et al. 2004; Yankner and Lu 2009). While too numerous to describe in detail here, proposed interaction partners for A β have included the serpin-enzyme complex receptor (SEC-R) and the insulin receptor, both of which are capable of binding to monomeric A β , although the physiological effects are unclear (Verdier and Penke 2004). Fibrillar A β , on the other hand has been shown to bind a wide array of cell-surface proteins, including the receptor for advanced glycation end products (RAGE) complex and the amyloid precursor protein (Verdier and Penke 2004), leading in some cases in increased radical formation and oxidative stress. Similarly, binding to the α -7 nicotinic receptor can mediate N-methyl-D-aspartate (NMDA) receptor activity, with broad effects on cellular metabolism (Snyder et al. 2005). Any or all of these effects may play a role in loss of synaptic function, leading to symptomatic Alzheimer's disease. Other proposed interactions, such as dysregulation of calcium channels, may be confounded by membrane disruption effects, making them harder to confirm.

Less is known about potential interactions of soluble oligomers with cell surface receptor molecules, although similar targets to the fibrillar material have been proposed. An intriguing possibility arises from recent reports that oligomeric A β binds to the unstructured N-terminus of cellular PrP, with initial reports suggesting that the toxic effects of small A β oligomers may be mediated by this interaction (Lauren et al. 2009). If true, such an association may lead to an alteration of the as yet unidentified signaling functions of PrP, or may allow PrP to act as carrier for internalization of oligomeric A β . In this model, once inside the cell, the prefibrillar oligomers would exert loss of function effects on internal cellular components through mechanisms not yet identified. While this observation may provide a tantalizing link between two neurodegenerative disorders, more work need to be done to confirm the specificity of the interaction, and to define the potential role played by PrP.

It is important to note that since A β exists *in vitro* and *in vivo* as a continuum of different oligomeric states, none of which are particularly stable, it is difficult to distinguish biological effects induced by one specific type of non-fibrillar oligomer. Therefore, it is entirely feasible that A β has significantly different physiological effects when in different oligomeric forms. Thus, it is difficult to exclude any of the putative mechanisms for involvement of A β oligomers in progression of amyloid disease without further study.

4.2 PrP(106-126) toxicity

There have been conflicting reports on the toxicity of PrP(106-126) largely due to confounding effects of its ability to form amyloid oligomers as well as potentially playing a role in conversion of full-length PrP to the infectious PrP^{Sc} form (Gu et al. 2002). PrP(106-126) has been shown to be toxic in a number of different ways. Reports initially characterized PrP(106-126) as requiring full-length PrP for toxicity in cerebral endothelial cells (Deli et al. 2000). There is also significant evidence for PrP-independent cytotoxicity,

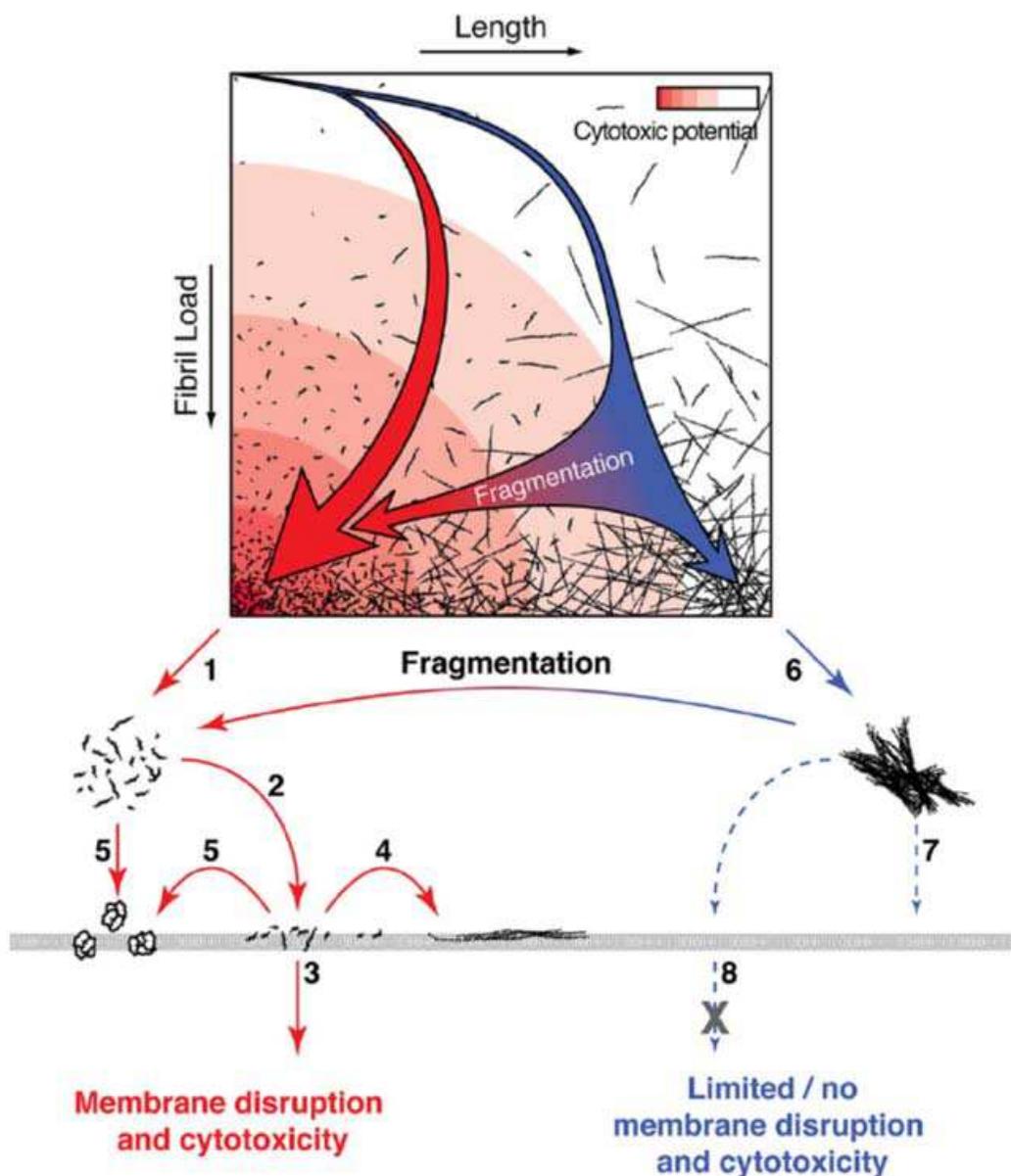


Fig. 5. The relationship between amyloid fibril length and toxicity. As the concentration of small fragments increases, increased membrane disruption and cellular toxicity are observed. As the fragments become smaller, it is proposed that they will be increasingly toxic to the cell. Reprinted with permission from Xue *et al.*, 2009. Copyright 2009 The American Chemical Society

but it is important to note that in most studies of PrP(106-126), the aggregation state of the peptide was not clearly defined, so the activity of prefibrillar oligomers is implicit rather than explicit in the results. PrP(106-126) has been shown to interact with L-type voltage sensitive calcium channels, causing apoptosis (Florio *et al.* 1998; Silei *et al.* 1999; Thellung *et al.* 2000). It has also been demonstrated that this peptide causes the activation of the JNK-c-Jun pathway, leading to apoptosis shortly after peptide treatment (Carimalo *et al.* 2005). There have been several reports of direct membrane destabilization by PrP(106-126), including the formation of ion channels (Lin *et al.* 1997), or alterations in membrane viscosity (Salmona *et al.* 1997). More recent work using well-defined prefibrillar oligomers

of PrP(106-126) have shown that it causes permeabilization of model membranes (Kayed et al. 2004; Walsh et al. 2009) and induces cytotoxicity in neuroblastoma cell cultures (Kayed et al. 2003). It is well known that PrP(106-126) interacts with phospholipid membranes even as a monomeric peptide, with lipid composition playing a role both in interaction and post-binding events. For example, PrP(106-126) has been shown to cause the aggregation of liposomes containing the ganglioside GM1 (Kurganov et al. 2004). While there is no direct link to the disruption of calcium channels or activation of the JNK-c-jun pathway, current evidence supports direct membrane interaction and disruption as a mechanism for PrP(106-126) cytotoxicity – at least in the absence of cell surface PrP. While unlikely in the face of recent studies for A β oligomers that show that structural alterations of the membrane are sufficient to increase conductance without requiring channels, rearrangement of the protein in the membrane to form discrete pores or channels cannot be ruled out (Eliezer 2006; Sokolov et al. 2006).

In terms of the structure-function relationship of PrP(106-126) oligomers, the similarities between the peptide subunits within the oligomeric and fibrillar forms of this protein are reminiscent of the large oligomers of A β (1-40) described by Chimon *et al.* (Chimon et al. 2007). Similar to one of the hypotheses proposed for A β , the insertion of small fibril fragments into the membrane may directly disrupt the membrane, nucleate the assembly of membrane-disruptive amyloid fibrils, or potentially rearrange into a toroidal or barrel stave type pore. In either case, the structural data supports the possibility of a common mechanism of action linking large spherical oligomers of A β and PrP(106-126).

4.3 α -synuclein toxicity

The toxicity associated with α -synuclein appears to be slightly different than other amyloid systems. To start with, α -synuclein is significantly larger (140 amino acids) than A β (40 or 42 residues), amylin (37 residues), or many other amyloidogenic proteins. Additionally, in its native state α -synuclein is intrinsically disordered, gaining α -helical structure upon binding to phospholipid membranes (Weinreb et al. 1996; Eliezer et al. 2001; Ulmer et al. 2005). In Parkinson's disease, α -synuclein forms β -sheet rich aggregates, culminating in the formation of amyloid fibrils (Lashuel et al. 2002; Lashuel et al. 2002). Not surprisingly, given its innate propensity to interact with membranes, the cytotoxic oligomers of α -synuclein have been shown to physically alter the conductance of planar bilayer membranes, presumably through the formation of pores (Kim et al. 2009). Multiple conductance levels were observed upon addition of these spherical, 15-30 nm diameter oligomers to lipid bilayers. The conductance profiles were similar to those observed for bee-venom mellitin, further supporting the formation of amyloid pores by these oligomers. Intriguingly, these pore-forming α -synuclein oligomers were recognized by the A11 antibody, which is specific for prefibrillar oligomers, suggesting that there are some common structural features shared with other amyloid oligomers, and providing an additional argument in favor of direct membrane disruption by prefibrillar oligomers.

5. Conclusion

It is clear that despite significant advances in the past decade, the link between accumulation of amyloidogenic proteins as β -sheet rich oligomers and disease pathogenesis remains somewhat unclear. In particular, the mechanism or mechanisms through which

various non-fibrillar oligomers are capable of inducing cell death remain to be unambiguously determined. This is inextricably linked to questions of disease relevance – do all of the oligomers observed *in vitro* play a role in cell death during amyloidosis, and do they act through the same mechanisms? While the concept of a common mechanism of amyloid toxicity is attractive, given the broad range of cellular and tissue level effects reported to date, it may represent an oversimplification of a complex system.

Certainly it is possible that despite some common structural motifs and a shared ability to physically disrupt membranes, different oligomeric species formed by different amyloid proteins may exert a range of activities, all leading to the same effective endpoint – cell death and degenerative disease progression. Additional questions surround the fibril-like structures observed in most toxic amyloid oligomers described to date. Does this relate to studies showing that fragmentation of amyloid fibrils can create cytotoxic, membrane disrupting species, or are these fibril fragments acting via distinct pathways from prefibrillar oligomers? Ongoing efforts in structure determination of oligomers formed by different amyloid proteins, and in defining the molecular mechanisms for their cytotoxicity, will be required in order to address these important questions and to elucidate the link between structure and toxic function.

6. References

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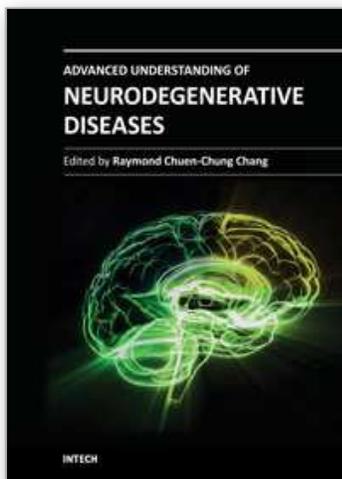
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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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